

**Final Progress Report**

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**Neural Prosthetic Control**

**NINDS CONTRACT NUMBER: N01NS92322**

**Department of Neuroscience and Brain Science Program**

**Brown Medical School**

**Brown University**

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**Final Report****Introduction**

During the course of this contract we showed that Bionic intracortical electrode arrays could provide neural activity from neurons in motor cortex for long periods, that this activity could be decoded into a reasonable replica of hand trajectory or into robot arm movement and that monkeys could use cortical signals for goal directed behavior, via a computer interface. Decoding methods based upon linear regression were developed and implemented to show that neural motor intention could be decoded 'open loop' into discrete motor output or continuous hand motion. In addition, closed loop control, in which signals could be used in real time to achieve goal directed behavior was implemented. The neural activity was decoded using a linear regression equation that required only a few minutes of hand motion to construct filter coefficients. This decoding was sufficiently good that it could immediately substitute for the actual hand control signal without intervening training. Thus, decoding and implementation could be achieved in approximately the same time as the neural driving of actual hand motion (on the order of 200 ms). As few as 6 neurons could be used to achieve control, although control improved with additional neurons; estimates are that around 20 randomly selected neurons in MI arm area will provide reasonable reconstruction of hand trajectory. These results reflect significant advances in: A. the ability to record many neurons at once using a device that has well-controlled manufacturing and design features, B. mathematical tools and sufficiently fast computers to deal with decoding of complex data in near real time, C. implementation of a neuromotor prosthetic device that is a reasonable prototype for a human neural prosthetic device.

**I. Objectives**

The overall objective of this contract was to develop a means to bring a robotic arm under near real time neural control using a recording device implanted in a macaque monkey motor cortex. These goals were largely met during the contract period.

*Summary of Contract Goals*

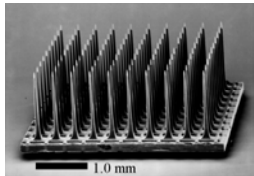
- 1. Identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex.**
- 2. Evaluate the form and amount of information available about movement kinematics from population recordings and demonstrate ability to mimic movement with a robotic arm.**
- 3. Identify algorithms for rapid decoding to allow near real time decoding of cortical signals.**
- 4. Demonstrate the ability of a macaque monkey to control movement of a robot arm.**

Progress in each of the specific goals:

### 1. Identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex

The goal of the array development of this aspect of the project was to identify the optimal properties and implantation procedures for Bionic/Utah electrode arrays to ensure long term, reliable recordings in macaque monkey cortex. This required monkey training in novel behavioral tasks, implantation method testing using various modifications in the surgical procedures and in the array assembly and recording to test the quality and stability of units.

**Arrays:** Arrays were implanted in the MI arm representation, medial and posterior to the spur of the arcuate sulcus, abutting the central sulcus. The ability to locate arm-related neurons using these sulcal landmarks has been 100% successful in our tests. We have used only one version of the Bionic microelectrode array, consisting of 100, 1.0 or 1.5 mm long platinized tip, silicon probes arranged in a square grid on 400 $\mu$ m centers, so that the overall size of the platform is 4 x 4 mm. Impedances between 50-1000 k $\Omega$  (median  $\sim$  300 k $\Omega$  @ 1 nA, 1kHz sine wave) were tested for efficacy. The data analyzed to date suggests that successful neural recording is not heavily dependent on the impedance- there has been no systematic relationship identified with the probability of successful recordings, except for electrodes with the lowest impedances ( $\sim$ 5 k $\Omega$ ) which have poor signal to noise ratio. Recent data, which will considerably increase the overall sample from improved electrodes, have not yet been systematically evaluated and may provide additional information concerning ideal impedance. All arrays are wired to connectors contained in a custom-designed titanium percutaneous pedestal using 1 mil gold. The number of wires and the connector type has been changed during the course of the project. Because tethering by the stiffness produced by large numbers of wires was thought to be a problem, tests were made with increasing numbers of wires. In addition, suitable connectors to support large numbers of wires were not available at the beginning of this contract period. One, called the NeuroPort has been developed. A list of connectors tested is presented in table 1.



## IMPLANTS: Data Summary

Connector Types

Microtek

Winchester

Tulip

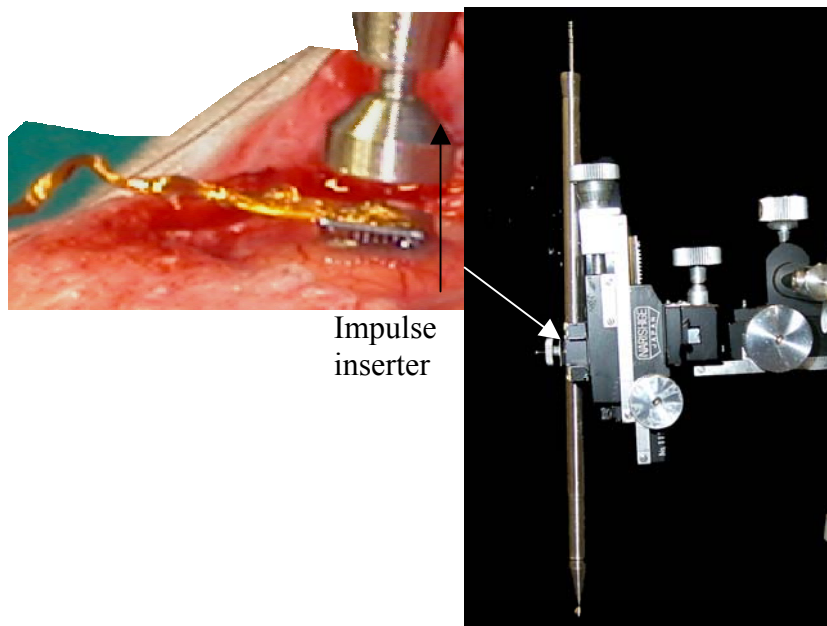
NeuroPort

Number of Monkeys Implanted	23	
Number of implants	<b>30</b>	
BIONIC	27	
other	(3)	
Microtek (11)	8	Too few connex
Winchester (47)	5	Bulky, bad fit
Tulip (36)	10	Fragile, only 36
Neuroport(96)	5	Successful, all electrodes connected
Number of Recording Days:	up to 1098 NP up to 120	
Histological processing	7	Under analysis

TABLE 1.

The initially available connector was a 12 pin Microtek, which allowed connection to only 11 electrodes (+ reference electrode) of the 100 available in the array. To increase recording to 22 we used two of these connectors. Subsequently we adopted a Winchester 50 pin connector. This connector is bulky and it is difficult to fabricate a universal pedestal that seats properly on the skull of different animals. Costs of custom fabrication were prohibitive. BTI (now Cyberkinetics, Inc or CKI) developed a new generation of 45 pin connectors, called the *tulip* connector, which is based upon an edge card connector. With two of these connectors we achieved 74 connections (with two references). These connectors have been problematic for several reasons. One is that the connector profile is high and the edge card and contacts are easily damaged. In addition, the gold connections are prone to wear. Connectors failed either when they rotated in the pedestal, thereby shearing all of the wires, or when contacts shorted. A major development during this project was the initial testing of a 96-channel low insertion force (contact) Neuroport connector (table 1, above) completed in 5 implants during the last 2 quarters. Successful recordings have been obtained from these implants, suggesting that this is a useful high-density connector, and that large numbers of wires do not produce significant tethering forces.

The work completed during this project also demonstrated the reliability of pneumatic insertion methods. All arrays were inserted rapidly into the cortex using a calibrated, pneumatically propelled mass (CKI). This has proved to be a reproducible insertion method based on the observation that successful recordings are reliably obtained.



We also tested the ability to explant arrays. Two arrays have been implanted and then removed, with an intervening period of several weeks (4 and 12 weeks each) between re-implantation. A third array placed in the same site is successfully recording, indicating that the arrays can be safely removed if required.

*Recording Quality and Stability:*

There were significant advances in the quality of recording during the contract period, which seems to be correlated with the insulating material used to coat electrodes. The first series of arrays were coated with polyamide (Microtek and Winchester series) while the tulip series were mainly silicon nitride coated. All neuroport series were parylene coated. Cells were recorded from 10% to over 70% of the available electrodes on an array with a mean of 40%. Signal to noise was similar with the first two coatings, but all of the parylene arrays have considerably better signal to noise ratio, with up to 120 neurons being detected on 91 possible channels in one test.

The ability to maintain the same cells each day of recording is important in the design of a prosthetic device. Recordings have been made as long as 1089 days after array implantation and a number of recordings have been carried out for many months. However, in the data analyzed during this contract period, the number of cells present varied from day to day (but not within a day) indicating that the populations shift over time. It is difficult to ascertain whether the same neurons come and go repeatedly or whether different neurons appear and are lost over time because waveforms poorly differentiate neurons. (i.e. the same waveform can appear for different neurons and the same neurons can have markedly different waveforms). It is noteworthy that the markedly improved recordings with the parylene coated arrays may alter the interpretations of earlier arrays.

*Histological analyses:* The goal of histological analysis was to determine tissue reaction to Bionic array. Thionin cell stain and GFAP were used to test for glial reactivity. Several months after implantation there is little glial reaction at most sites, as measured by GFAP reaction product. Long term biocompatibility is also demonstrated by the ability to record neurons for years on these arrays. By qualitative measures these neurons appear to be no different in their properties from those recorded in acute preparations. Current arrays do however, sink 100 or more  $\mu\text{m}$  into the cortex, compressing the upper cortical layers; the functional effect of this is not detectable in our neural recordings.

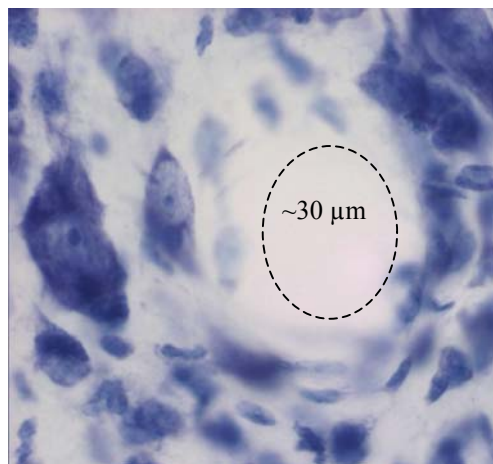
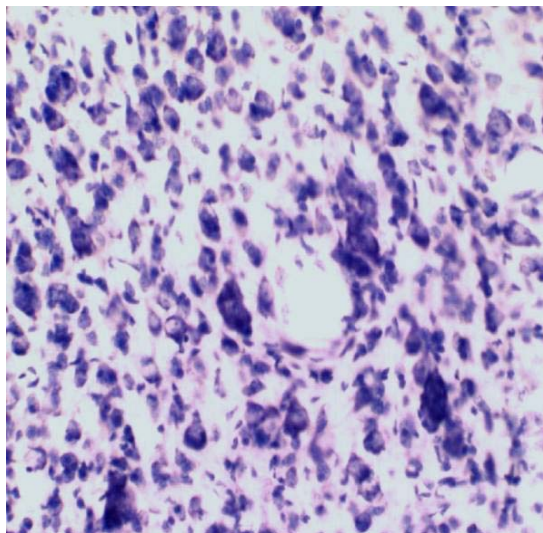
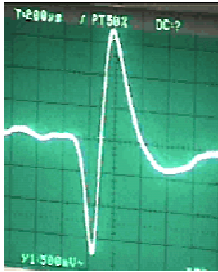


Figure 1. Thionin stain around penetration site at low and high power. Note neuron with well-formed nucleus and nucleolus to the left of the probe site. Implant duration 1 month.



## **2. Evaluate the form and amount of information available about movement kinematics from population recordings and demonstrate ability to mimic movement with a robotic arm.**

We initially showed that a robot arm could mimic targeted discrete directional movements using a discrete, probabilistic decoding method. Barinaga reported this early result in *Science* magazine in 1999. We later were able to achieve real-time closed-loop direct neural control over a computer cursor in two macaque subjects. We showed how activity from a few (7–30) MI neurons can be decoded into a signal that a monkey is able to use immediately to move a computer cursor to any new position in its workspace ( $14^\circ \times 14^\circ$  visual angle). The results with the first subject were reported in Serruya et al (2002). In both macaque subjects the following experiment was conducted: After a brief data acquisition period (2–3 min), a linear filter decoding model was built which was subsequently used to provide direct neural control over the computer cursor. Both monkeys achieved direct neural control immediately after model construction. We found that cursor control was nearly as good as direct hand-positional control. The time required to acquire targets using the neural signal was only slightly greater than that required for hand motions; this difference was not significant at  $\alpha = 0.05$  by a two-sided Kolgorov–Smirnov test. By contrast, target acquisition was unsuccessful ( $> 1$  min) if filters were randomly shuffled between cells or if a random number was added to the filter coefficients, indicating that properly constructed filters are necessary for neural control to operate. The marked, immediate success of the linear-regression method compared with other approaches may be related to the lack of strong assumptions about neuronal firing, to the power of the linear-regression method, or to the number and type of cells used for decoding.

After demonstrating that each subject could immediately acquire any target randomly positioned in the workspace, we went on to investigate whether neural trajectories resemble hand trajectories in a center-out task. Hand and direct neural control were alternated as the monkeys played a center-out task. Cursor trajectories under neural control were found to have more variance and took longer than those under hand control (t-test,  $\alpha = 0.05$ ). Comparison of trajectories generated under neural control with those derived of neural activity open loop indicate considerable improvement in cursor control may be achieved by visual feedback. Directional tuning of recorded units did not appear to change between the two modes of control. The immediate and accurate use of the neurally driven cursor implies that the decoding models are extracting sufficient information about motor intent that subjects do not have to actively modify neural tuning properties in order to achieve behaviorally useful control.

Our results demonstrate that a simple linear weighting approach, coupled with the participating primate subject, can provide a behaviorally useful pointing control signal with neural-machine interfaces may eventually find application in helping neurologically impaired humans.

### **3. Identify algorithms for rapid decoding to allow near real time decoding of cortical signals.**

The goal of this aspect of the project was to determine whether the reconstruction of hand trajectory using the activity of multiple MI neurons can be both reliable enough and performed *fast* enough to be used in a prosthetic device.

Linear decoding, which consists in regressing separately the  $x$  and  $y$  coordinates of hand position at time  $t$  on the observed spike counts of the simultaneously recorded neurons in a given, suitably discretized, time window before time  $t$ , is one of the simplest and fastest methods available—if not the fastest. However, it is limited in its accuracy. Indeed, it works best with relatively long time windows (typically 1 or 2 sec): "integrating" the neural signal over a long window in effect compensates for the fact that this method does not include an explicit model of the hand dynamics that would ensure smoothness of the reconstructed trajectory. The drawback is of course a loss in the spatio-temporal resolution of the reconstruction. We first reported the use of linear decoding to reconstruct hand trajectories at the annual meeting of the Society for Neuroscience in 1999 (Paninski, et al, 1999).

At the other hand of the model-complexity spectrum lie non-parametric models, which include both a *prior* probability that encodes our expectations about the variation of neural activity in velocity or position space, and a explicit model of the *temporal dynamics* of the position and/or velocity state, essentially a Markov chain in which the state at a given time depends only on the state at the previous time instant. While more powerful and providing a potentially higher resolution, these non-parametric models are computationally quite demanding. Not only do they require off-line training of a family of non-parametric "tuning curves," they also use reconstruction methods, such as the standard "particle filtering" algorithm, which can be computationally heavy.

We have therefore investigated several intermediate solutions—in terms of complexity—using in particular the Kalman-filter framework, where the hand movement (position, velocity and acceleration) is modeled explicitly and *linearly* as the system state, and the observation, namely the firing rate in a 70-ms window, is also modeled as a linear function ("generative model") of the state (hand kinematics, including two position variables, two velocity variables, and, optionally, two acceleration variables) plus Gaussian noise.

Training the Kalman filter is fast, as it requires only the least-squares estimation of a 6x6 matrix (obtained by a single pseudo-inverse calculation), the least-squares estimation of a 6xC matrix (where C is the number of recorded neurons), and the estimation of the variance-covariance matrices for the two noise terms. We found that approximately 3.5 minutes of training data suffices for accurate reconstruction. On-line reconstruction is instantaneous, as it is recursive and involves only a very simple update.

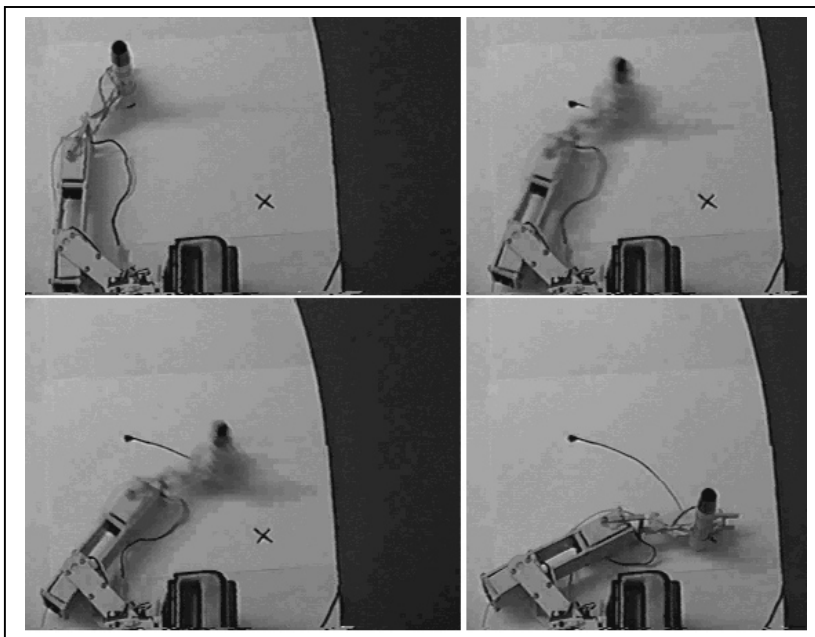
The accuracy of the method is assessed by reconstructing test trajectories off-line using recorded neural data not present in the training set. Experimental results showed that the Kalman-filter approach is more accurate than linear filtering, under every error measure that was tried. While linear filtering is extremely simple, it lacks many of the desirable properties of the Kalman filter. The method requires long windows in which to collect data. For rapid motions, this long time

window is inappropriate yet smaller time windows lead to very inaccurate results. Additionally, the linear filter does not make the system dynamics and noise models explicit.

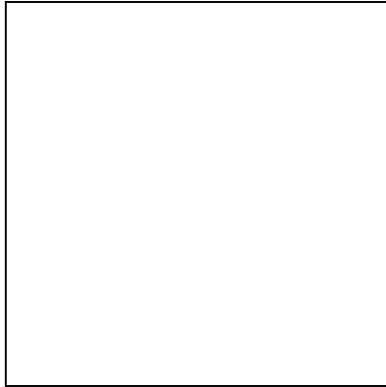
In contrast, the Kalman filter provides an explicit generative model, a clear probabilistic interpretation, an incremental estimate of the state that improves over time, and an estimate of the uncertainty in the state. Computationally, the Kalman filter is simple to train and the real-time implementation of tracking is trivial. Additionally, the framework allows the analysis of optimal lag times in the generative model, which result in improved state estimates.

#### **4. Demonstrate the ability of a macaque monkey to control movement of a robot arm.**

In 1999 Mijail Serruya demonstrated that offline Bayesian classification of neural activity recorded during a center-out task could be used to drive a LynxMotion 5-axis robotic arm in the predicted direction. This experiment marked a proof-of-concept that multi-electrode recorded activity from a primate could be used to drive a physical device. This work, including a photograph of the robotic arm being driven by the neural activity, is cited in Barinaga, 1999. While the problem of activating a device using a computer output is trivial compared to the problem of decoding a useful signal from neural data, it does foreshadow the question of how much post-hoc processing output devices ought to conduct. Using a lookup table to launch ballistically to pre-defined target positions may suffice for the laboratory, but what about a robotic arm navigating in a patients' home or workplace? The idea of providing simply a high-level command, i.e. specifying a target zone, may be appealing because the lookup table specifies the actual device function, or with more elaborate robots, the robotic controller cards solve inverse kinematics. The amount of movement specification detail will continue to be a debate in neuromotor prosthetics for human use. While it may initially sound more attractive to generate only intended target positions from cortex, and let the robot solve the inverse kinematic problems, it may be that we are throwing away information present in the cortical signal about joint positions, torques and perhaps other kinematic or dynamic features that patients may learn to master if combined sensibly with a robotic arm.



ROBOT ARM Directed to discrete target using decoded neural activity (Barinaga, Science 1999)



CRS Robot Arm

From 2000-2001 we developed a direct neural-robot interface using a CRS robotic arm. Ammar Shaikhouni wrote software in Labview to transform the neurally decoded trajectory signals into commands for the CRS robot arm with data streamed from another computer. We had to implement several software workarounds to deal with the CRS robot position hardware, which did not lend itself to continuous position updating. The speed control architecture of the CRS robot precluded rapid updating, however, this robot arm could be driven in near real time (approximately 200-300msec delay) from neural activity being decoded from a macaque using closed-loop control of a computer cursor. The subject was not aware of the robotic arm in this project, but instead controlled the cursor. The robotic arm successfully followed the neurally controlled cursor.

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### **Recommendations for Future Research**

There should be continued development of neural interfaces and signal processing technology, computational and mathematical decoding methods and human interfaces for prosthetic control. High density cabling that is very flexible, and micro scale signal conditioning and processing and telemetry are needed, as are micro scale computational processing devices that can handle the complexities of signal decoding. Additional signal decoding that can deal with higher dimensional problems of control (such as finger movement) would also be useful. Finally, it is also critical to develop interfaces that will be of maximal benefit to patients; agreement on the optimal first and later generation patient devices should be considered.

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